IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES, L.P. and TCD ROYALTY SUB LP Plaintiffs, v. LUPIN INC. and LUPIN LIMITED Defendants.	)	C.A. No. 21-cv-01710-SB **REDACTED - PUBLIC VERSION**

DEFENDANTS LUPIN INC. AND LUPIN LIMITED'S DAUBERT MOTION TO PRECLUDE DR. RUDNIC'S THEORY OF LUPIN'S COMPOSITION RATIO BASED ON DAY 1 PLASMA CONCENTRATIONS AND MEMORANDUM IN SUPPORT THEREOF

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Lupin respectfully requests that the Court preclude Galderma and its expert, Dr. Rudnic, from offering any opinion that a person of ordinary skill in the art could infer Lupin's composition ratio from mean plasma concentration data. As detailed below, based on each and every one of the eight *Daubert* factors, Dr. Rudnic's novel theory is simply not reliable.

- **Testable Hypothesis?** Dr. Rudnic did not test his unprecedented theory; instead, he testified it would be "extremely difficult" to do so. (*infra* ¶¶ 15-16)
- **Peer Review?** No evidence of peer review. (¶ 17)
- **Error Rate?** No evidence of rate of error. (¶ 18)
- **Standards?** No evidence of any applicable standard. (¶ 19)
- **Generally Accepted?** No evidence of general acceptance. (¶ 20)
- **Related to a Reliable Method?** There is no evidence that Dr. Rudnic's theory is based on any reliable method, such as an *in vitro*/*in vivo* correlation model. (¶ 21)
- **Qualifications?** No evidence of correlation modeling qualifications. (¶ 22)
- **Non-Judicial Uses?** No evidence of use outside this Lupin case. (¶ 23)

I. BACKGROUND

1. The asserted patents require a composition ratio of about 30 mg immediate release to about 10 mg delayed release:

532 Patent	740 Patent
1. An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml, the composition consisting of (i) an immediate release (IR) portion comprising a drug, wherein the drug consists of about 30 mg doxycycline; (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least one enteric polymer; and (iii) one or more pharmaceutically acceptable excipients.	1. An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 µg/ml and a maximum of 1.0 µg/ml, the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.

532 Patent (Exhibit 1); *740 Patent* (Exhibit 2).[1]

2. [redacted]

[redacted]

3. Neither Galderma nor Dr. Rudnic contend that Lupin's label is false or misleading. *See, e.g.*, *Galderma Statement of Facts* (Exhibit 4); *Rudnic Deposition* (Exhibit 5) at 153:14-154:9, 164:3-170:18; *Rudnic DX-9* (Exhibit 6) at 11, 19, 20.

4. Both Galderma and Dr. Rudnic concede that, using the industry standard test described in the asserted patents, [redacted] *See, e.g.*, *Galderma Statement of Facts* (Exhibit 4) ¶ 100; *Rudnic Deposition* (Exhibit 5) at 13:8-14:10; *Rudnic DX-46* (Exhibit 7); *Rudnic DX-47* (Exhibit 8); *532 Patent* (Exhibit 1) at Figures 1-3.

5. To be clear, there is no dispute that, using the pH 1.1 test condition described and exemplified in the patents, Lupin's composition would not infringe any asserted claim because the undisputed test data prove [redacted] *See, e.g.*, *532 Patent* (Exhibit 1) at Figure 1 (immediate release measured at pH 1.1 at 10, 20 and

[1] Highlights and emphasis have been added, unless otherwise noted.

30 minutes); Figure 2 (immediate release measured at pH 1.1 at 60 and 120 minutes); Figure 3 (immediate release measured at 60 and 120 minutes); *Galderma Statement of Facts* (Exhibit 4) ¶ 100 [redacted]

6. Neither Galderma nor Dr. Rudnic dispute any of the data proving that, using the test conditions and timepoints in the asserted patents, [redacted]

Rudnic DX-32 (Exhibit 9) at LDOX12468-76.[2]

7. Instead of disputing the test data, Galderma and Dr. Rudnic offer a new and obscure theory that a POSA could interpret plasma concentrations to suggest that Lupin's composition immediately releases about 30 mg. *See, e.g.*, *Galderma Statement of Facts* (Exhibit 4) ¶¶ 186, 189-190, 254-255, 260; *Rudnic Deposition* (Exhibit 5) at 273:24-295:23. More specifically, Dr. Rudnic relies on the following presentation of data over 96 hours for his theory:

[2] In the previous doxycycline cases against Amneal and Sun, both Galderma and Dr. Rudnic relied on test conditions in the asserted patents to determine the ratio of the accused compositions—*i.e.*, pH 1.1 at 30 minutes. *See, e.g.*, *Rudnic DX-29* (Exhibit 10) at 34:9-20, 35:25-36:5, 124:1-125:17, 164:16-23; *Rudnic DX-30* (Exhibit 11) at 361:23-363:7.

Galderma Statement of Facts (Exhibit 4) ¶ 98.

8. Dr. Rudnic agrees that, in a fasted stomach, the residence time of the compositions at issue (*i.e.*, the immediate release period) is about 30-60 minutes. *Rudnic Deposition* (Exhibit 5) at 80:18-20, 104:12-19.

9. When the Day 1 mean plasma concentration data presented above is examined closely on a 4-hour scale, one can observe differences between ORACEA and Lupin's composition, for example, at the 20-minute, 40-minute and 60-minute timepoints:

Rudnic DX-44 (Exhibit 12).

10. In his deposition, when presented with the datapoints and differences above, Dr. Rudnic admitted that he is unable to determine the mean concentration values that he believes [redacted] would produce at any timepoint, including the 20-, 40- and 60-minute timepoints. *See Rudnic Deposition* (Exhibit 5) at 290:2-294:13, 295:15-23.

* * *

II. LEGAL STANDARD

A. Federal Rule of Evidence 702

11. Rule 702 provides, in part, that an expert may testify in the form of an opinion if:

> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

B. *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993)

12. To be admissible, an expert's testimony must rest on a reliable foundation. *See 10x Genomics, Inc. v. NanoString Techs., Inc.*, No. 21-653, 2023 WL 5805585, at *7 (D. Del. Sept. 7, 2023) (citing *Daubert*). "In order to be reliable, expert testimony must have 'a grounding in the methods and procedures of science.'" *Warner Chilcott Labs. Ireland Ltd. v. Impax Labs., Inc.*, No. 08-6304, 2012 WL 1551709, at *24 (D.N.J. Apr. 30, 2012). "In other words, determining whether expert evidence is reliable 'requires a determination as to its scientific validity.'" *Id.*

13. The Third Circuit has articulated eight "non-exclusive factors to consider when deciding whether to admit evidence as 'reliable' under Rule 702 and *Daubert*: (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put." *Id.* (quoting *U.S. v. Mitchell*, 365 F.3d 215, 235 (3d Cir. 2004)).

* * *

III. ARGUMENT

14. Based on the following eight factors, Lupin respectfully submits that Dr. Rudnic's theory of composition ratios based on Day 1 mean plasma concentration data does not meet the *Daubert* standard, and should be precluded as unreliable.

A. Whether a method consists of a testable hypothesis.

15. Neither Galderma nor Dr. Rudnic have identified any "method" for inferring or calculating a composition ratio from mean plasma concentration data. *See, e.g.*, *Galderma Statement of Facts* (Exhibit 4) ¶¶ 186, 189-190, 254-255, 260; *Rudnic Deposition* (Exhibit 5) at 273:24-295:23. For example, Dr. Rudnic testified—evasively—as follows:

> Q: Dr. Rudnic, are you suggesting that a POSA could infer the ratio of Lupin's composition from mean concentration data?
>
> A. **Not alone**, you'd have to use a lot of other information to come to that conclusion.
>
> Q: Are you suggesting that a POSA could calculate the ratio of Lupin's composition from mean plasma concentration data?
>
> A: **No**, that's one piece of many pieces of information that you would need to come to that conclusion.
>
> Q: What method would a POSA use to calculate the ratio of Lupin's composition from mean plasma concentration data?
>
> A: **I'm not sure**, but that is just simply one of several pieces of information that you would need to come to that conclusion.
>
> * * *
>
> Q: Are you aware of any method that will allow someone to attempt to infer composition ratios from mean concentration data?
>
> A: **Not in a vacuum.** You have to use it in the combination of in vitro, batch record, other absorption data on doxycycline, and you use it all in concert to fill in answers to the **puzzle**. This is also one piece to the **puzzle**.

Rudnic Deposition (Exhibit 5) at 274:25, 281:11; *see also id.* at 295:8-13 (also referring to the "puzzle" as a "mosaic").[3]

16. Even if Dr. Rudnic had identified a "method" underlying his hypothesis, he did not test his hypothesis; he believes it would be "extremely difficult"; and he was unable to calculate or even estimate the mean concentration data that he believes [redacted] would produce. *See Rudnic Deposition* (Exhibit 5) at 285:18 ("I don't believe it's impossible, I just think it's **extremely difficult**."), 286:19 ("I said it would be **extremely difficult** to do."), 287:11-21 (did not conduct any mathematical comparisons of the mean concentration data), 288:4-295:23 (unable to calculate or estimate mean concentration data for [redacted] Ultimately, Dr. Rudnic suggested that he did not need to test his hypothesis. *Id.* at 295:15 ("Q: I just want a clear record. If you don't know the mean concentration curve that [redacted] would produce, how can you draw conclusions about composition ratios from this mean concentration data? A: I don't need to. . . .").

B. Whether the method has been subject to peer review.

17. There is no evidence that Dr. Rudnic's "method" of attempting to infer composition ratios has been subject to peer review. *See Rudnic Deposition* (Exhibit 5) at 281:20-24.

C. The known or potential rate of error.

18. There is no evidence that Dr. Rudnic's "method" of attempting to infer composition ratios has a known rate of error. *See Rudnic Deposition* (Exhibit 5) at 281:25-282:5.

[3] Instead of identifying a method, Dr. Rudnic attempted to obscure the absence of math and science by referring to what he called a "puzzle" or "mosaic." But a "puzzle" or "mosaic" is not a hypothesis that is capable of being proved false by a mathematical or scientific method. *See Warner,* 2012 WL 1551709, at *24 ("The first factor, 'testability,' asks whether the proposition is at issue is 'capable of being proved false.').

D. The existence of standards controlling the technique's operation.

19. There is no evidence that Dr. Rudnic's "method" of attempting to infer composition ratios is based on any standard or technique. *See Rudnic Deposition* (Exhibit 5) at 282:6 ("Q: To your knowledge, is there any standard or technique that governs a method of attempting to infer composition ratios from mean concentration data? A: It is one piece of the **puzzle**, not individually it tells you how to do it, you have to look at it in the context of all the information that's provided to you. It's one piece of the **puzzle**, not everything.").

E. Whether the method is generally accepted.

20. There is no evidence that Dr. Rudnic's "method" of attempting to infer composition ratios has been generally accepted. *See Rudnic Deposition* (Exhibit 5) at 282:16-283:2.

F. The relationship of the technique to methods which have been established to be reliable.

21. There is no evidence that Dr. Rudnic's "technique" of attempting to infer composition ratios is based on any reliable method, such as any of the industry standard methods of modeling any *in vitro*/*in vivo* correlation. *Rudnic Deposition* (Exhibit 5) at 283:14-286:4; *Rudnic DX-36* (Exhibit 13) at 3, 5-6 ("Developing the Correlation").

G. The qualifications of the expert witness testifying based on the methodology.

22. There is no evidence that Dr. Rudnic's "method" of attempting to infer composition ratios is based on any background, education or qualifications in the mathematics or science of correlating mean plasma concentrations to pharmaceutical composition ratios. *See Rudnic Deposition* (Exhibit 5) at 286:14 ("Q: So with respect to this compound in this case, doxycycline, you consider yourself an expert in correlation of mean plasma concentrations to pharmaceutical composition ratios? A: **No**, I said it would be extremely difficult to do.").

H. The non-judicial uses to which the method has been put.

23. There is no evidence that Dr. Rudnic's "method" of attempting to infer composition ratios has been used outside of this litigation. *See Rudnic Deposition* (Exhibit 5) 286:21-287:10.

IV. CONCLUSION

24. Dr. Rudnic's attempt to reverse-engineer an infringing composition ratio from mean plasma concentration data fails each and every one of the *Daubert* tests outlined above. Lupin respectfully submits that Galderma and Dr. Rudnic should be precluded from offering any opinion that a person of ordinary skill in the art could infer Lupin's composition ratio from Day 1 mean plasma concentration data. If Dr. Rudnic cannot calculate—or even estimate—the Day 1 mean plasma concentration data for what he would consider to be [redacted] In short, Dr. Rudnic's circular argument is not science.

* * *

Dated: October 13, 2023

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CERTIFICATE OF SERVICE

I, Megan C. Haney, Esquire, hereby certify that on October 13, 2023, a copy of Defendants Lupin Inc. and Lupin Limited's Daubert Motion to Preclude Dr. Rudnic's Theory of Lupin's Composition Ratio Based on Day 1 Plasma Concentrations and Memorandum in Support Thereof was caused to be served upon the following counsel in the manner indicated below:

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